

Rec'd PCT/PTO 18 MAR 2003  
PCT/EP 10543



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## Request for grant of a patent

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23 SEP 2002

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1. Your reference	4-32676P1		
2. Patent application number (The Patent Office will fill in this)	0222056.4 24SEP02 E750375-1 D00524 P01/7700 0.00-0222056.4		
3. Full name, address and postcode of the or of each applicant (underline all surnames)	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND		
Patent ADP number (if you know it) If the applicant is a corporate body, give the country/state of its incorporation			
4. Title of invention	Process For the manufacture of Organic Compounds 65096489 00 4		
5. Name of your agent (If you have one) "Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH		
Patents ADP number (if you know it)	1800001		
6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority application number (if you know it)	Date of filing (day/month/year)
7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)	
8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:  a) any applicant named in part 3 is not an inventor, or  b) there is an inventor who is not named as an applicant, or  c) any named applicant is a corporate body.  (see note (d))	Yes		

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Statement of inventorship and right to grant of a patent (Patents Form 7/77)  
Request for preliminary examination and search (Patents Form 9/77) ONE  
Request for substantive examination (Patents Form 10/77)  
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11. I/We request the grant of a patent on the basis of this application

Signature

Date

*B.A. Yorke & Co.*

23 September 2002

12. Name and daytime telephone number of person to contact in the United Kingdom  
Mrs. E. Cheetham  
020 8560 5847

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DUPLICATE

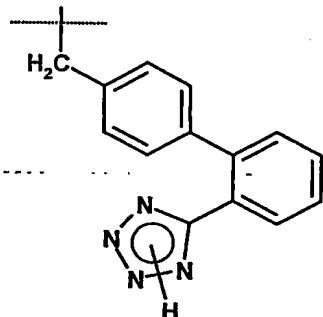
- 1 -

Process for the Manufacture of Organic Compounds

The present invention relates to a process for the manufacture of an angiotensin receptor blocker (ARB; also called angiotension II receptor antagonist or AT<sub>1</sub> receptor antagonist) and salts thereof, to novel intermediates and process steps. ARBs can, for example, be used for the treatment of hypertension and related diseases and conditions.

The class of ARBs comprises compounds having different structural features, essentially preferred are the non-peptidic ones. For example, mention may be made of the compounds that are selected from the group consisting of valsartan (cf. EP 443983), losartan (cf. EP253310), candesartan (cf. 459136), eprosartan (cf. EP 403159), irbesartan (cf. EP454511), olmesartan (cf. EP 503785), and tasosartan (cf. EP539086), or, in each case, a pharmaceutically acceptable salt thereof.

All of these ARBs comprise the following common structural element:



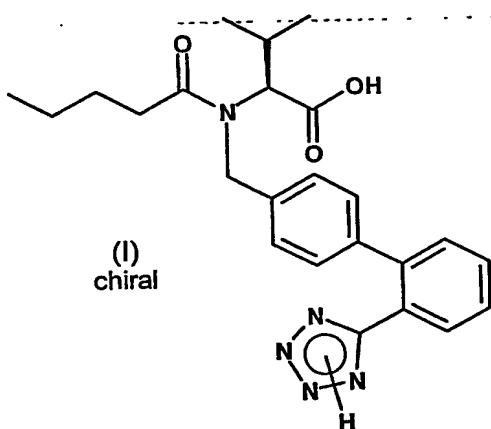
The formation of the tetrazole ring is a critical step in the manufacture of these compounds. Methods for the manufacture of ARBs having this structural feature include the formation of said tetrazole ring by starting from corresponding cyano derivatives that react with HN<sub>3</sub> or a suitable alkali metal salt thereof such as sodium azide or with an organotin azide such as tributyltin azide or with a silyl azide. The use of azides for forming the tetrazole ring system requires a sophisticated system to run the reaction in a safe way during an up-scaled production process. Accordingly, an objective is to develop alternative process variants that exclude the use of azides in the last steps of the production of corresponding ARBs.

The objective of the present invention is to provide a synthesis of compounds of formula (I) that (1) does not require a process step where an azide is used, (2) results in high yields, (3)

minimises pollution of the environment e.g. by essentially avoiding organotin compounds, (4) is economically attractive by using less reaction steps in the reaction sequence for the manufacture of compounds of formula (I), (5) affords enantiomerically pure target products and products of high crystallisability. In addition, as the tetrazole ring system is formed at an earlier stage of the reaction sequence, (6) the risk of contamination of the final product (and late intermediates) with trace amounts of tin components is much lower. Normally, the tetrazole ring is formed by reacting a corresponding cyano-derivative with an organotin compound such as tributyl tin azide. For ecological reasons, the heavy metal tin and especially organotin compounds are to be handled with special care. Furthermore, (7) another objective of the present invention is to provide a process that can be carried out on a larger scale and can thus be used for a corresponding production process and to avoid e.g. racemisation and thus separation of any enantiomers.

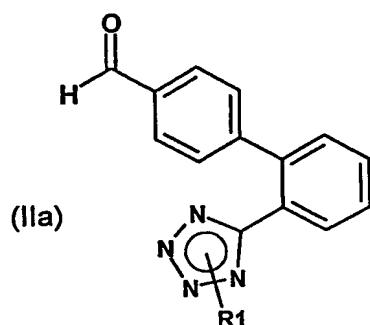
It has surprisingly been found that the process according to the present invention meets the above objectives.

The present invention relates to a process for the manufacture of the compound of formula (I)

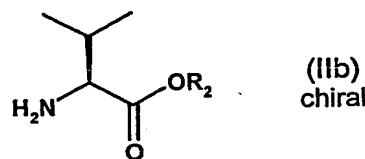


or a salt thereof, comprising

(a) reacting a compound of formula (II a)

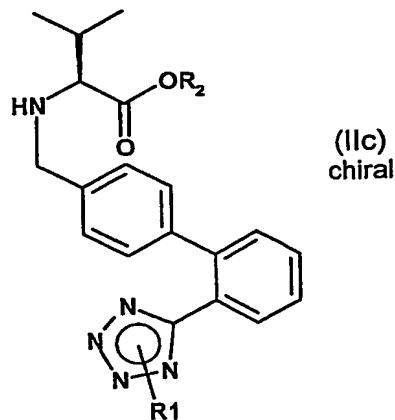


or a salt thereof, wherein R<sub>1</sub> is hydrogen or a tetrazole protecting group, with a compound of formula

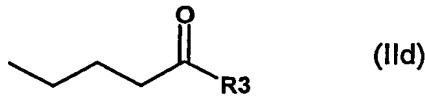


or a salt thereof, wherein R<sub>2</sub> represents hydrogen or a carboxy protecting group, under the conditions of a reductive amination; and

(b) acylating a resulting compound of formula (II c)

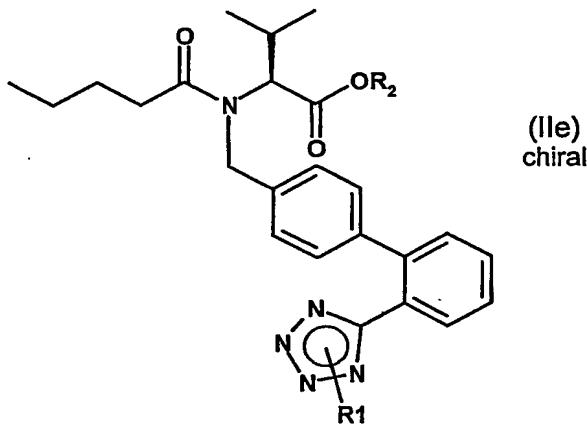


or a salt thereof with a compound of formula (II d)



wherein R<sub>3</sub> is an activating group; and,

(c) — if R<sub>1</sub> and/or R<sub>2</sub> are different from hydrogen, removing the protecting group(s) in a resulting compound of formula (II e)



or a salt thereof; and

(d) isolating a resulting compound of formula (I) or a salt thereof; and, if desired, converting a resulting free acid of formula (I) into a salt thereof or converting a resulting salt of a compound of formula (I) into the free acid of formula (I) or converting a resulting salt of a compound of formula (I) into a different salt.

The reactions described above and below in the variants are carried out, for example, in the absence or, customarily, in the presence of a suitable solvent or diluent or a mixture thereof, the reaction, as required, being carried out with cooling, at room temperature or with warming, for example in a temperature range from about -80°C up to the boiling point of the reaction medium, preferably from about -10° to about +200°C, and, if necessary, in a closed vessel, under pressure, in an inert gas atmosphere and/or under anhydrous conditions.

Compounds of formulae (II a), (II b), (II c) and (II e), wherein either or both of R<sub>1</sub> and R<sub>2</sub> are hydrogen can form salts with bases, as both the unprotected tetrazole ring and the

unprotected carboxy group have acidic properties, while while compounds of formulae (II b) and (IIc) can also form salts with acids.

A corresponding tetrazole protection group ( $R_1$ ) is selected from those known in the art. Especially,  $R_1$  is selected from the group consisting of tert-C<sub>4</sub>-C<sub>7</sub>-alkyl such as tert-butyl; C<sub>1</sub>-C<sub>2</sub>-alkyl that is mono-, di or trisubstituted by phenyl, such as benzyl or benzhydryl or trityl, wherein the phenyl ring is un-substituted or substituted by one or more, e.g. two or three, residues e.g. those selected from the group consisting of tert-C<sub>1</sub>-C<sub>7</sub>-alkyl, hydroxy, C<sub>1</sub>-C<sub>7</sub>alkoxy, C<sub>2</sub>-C<sub>8</sub>-alkanoyl-oxy, halogen, nitro, cyano, and trifluoromethyl (CF<sub>3</sub>); picolinyl; piperonyl; cumyl; allyl; cinnamoyl; fluorenyl; silyl such as tri-C<sub>1</sub>-C<sub>4</sub>-alkyl-silyl, for example, trimethyl-silyl, triethylsilyl or tert-butyl-dimethyl-silyl, or di-C<sub>1</sub>-C<sub>4</sub>-alkyl-phenyl-silyl, for example, dimethyl-phenyl-silyl; C<sub>1</sub>-C<sub>7</sub>-alkyl-sulphonyl; arylsulphonyl such as phenylsulphonyl wherein the phenyl ring is un-substituted or substituted by one or more, e.g. two or three, residues e.g. those selected from the group consisting of C<sub>1</sub>-C<sub>7</sub>-alkyl, hydroxy, C<sub>1</sub>-C<sub>7</sub>alkoxy, C<sub>2</sub>-C<sub>8</sub>-alkanoyl-oxy, halogen, nitro, cyano, and CF<sub>3</sub>; C<sub>2</sub>-C<sub>8</sub>-alkanoyl such as acetyl or valeroyl; and esterified carboxy such as C<sub>1</sub>-C<sub>7</sub>-alkoxy-carbonyl, for example, methoxy-, ethoxy- or tert-butoxy-carbonyl; and allyloxycarbonyl. Examples of preferred protective groups which may be mentioned are tert-butyl, benzyl, p-methoxybenzyl, 2-phenyl-2-propyl, diphenylmethyl, di(p-methoxyphenyl)methyl, trityl, (p-methoxyphenyl)diphenylmethyl, diphenyl(4-pyridyl)methyl, benzyloxymethyl, methoxymethyl, ethoxymethyl, methylthiomethyl, 2-tetrahydropyranyl, allyl, trimethylsilyl and triethylsilyl.

A corresponding carboxy protecting group ( $R_2$ ) is selected from those known in the art. Especially,  $R_2$  is selected from the group consisting of C<sub>1</sub>-C<sub>7</sub>-alkyl such as methyl, ethyl or a tert-C<sub>4</sub>-C<sub>7</sub>-alkyl, especially tert-butyl; C<sub>1</sub>-C<sub>2</sub>-alkyl that is mono-, di or trisubstituted by phenyl, such as benzyl or benzhydryl, wherein the phenyl ring is un-substituted or substituted by one or more, e.g. two or three, residues e.g. those selected from the group consisting of C<sub>1</sub>-C<sub>7</sub>-alkyl, hydroxy, C<sub>1</sub>-C<sub>7</sub>alkoxy, C<sub>2</sub>-C<sub>8</sub>-alkanoyl-oxy, halogen, nitro, cyano, and CF<sub>3</sub>; picolinyl; piperonyl; allyl; cinnamyl; tetrahydrofuranyl; tetrahydropyranyl; methoxyethoxy-methyl, and benzyloxymethyl. Examples of preferred protective groups which may be mentioned are ???

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The activating group  $R_3$  is, for example, halogen such as chlorine, fluorine or bromine; C<sub>1</sub>-C<sub>7</sub>-alkylthio such as methyl-thio, ethyl-thio or tert-butyl-thio; pyridyl-thio such as 2-pyridyl-thio; imidazolyl such as 1-imidazolyl; benzthiazolyl-oxy such as benzthiazolyl-2-oxy-;

benzotriazol-oxy such as benzotriazolyl-1-oxy-; C<sub>2</sub>-C<sub>8</sub>-alkanoyloxy, such as butyroyloxy or pivaloyloxy; or 2,5-dioxo-pyrrolidinyl-1-oxy. Examples of an activating group which may be mentioned are ???

The general terms used hereinbefore and hereinafter have the following meanings, unless defined otherwise:

C<sub>1</sub>-C<sub>7</sub>-Alkyl is for example methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl or a corresponding pentyl, hexyl or heptyl residue. C<sub>1</sub>-C<sub>4</sub>-alkyl, especially methyl, ethyl or tert-butyl is preferred.

C<sub>1</sub>-C<sub>7</sub>-Alkoxy is for example methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy, isobutyloxy, sec-butyloxy, tert-butyloxy or a corresponding pentyloxy, hexyloxy, or heptyloxy residue. C<sub>1</sub>-C<sub>4</sub>-alkoxy is preferred. Especially preferred is methoxy, ethoxy and tert-butoxy.

C<sub>2</sub>-C<sub>8</sub>-Alkanoyl in C<sub>2</sub>-C<sub>8</sub>alkanoyl-oxy is in particular acetyl, propionyl, butyryl, isobutyryl or pivaloyl. C<sub>2</sub>-C<sub>5</sub>Alkanoyl is preferred. Especially preferred is acetyl or pivaloyl.

Halogen is in particular chlorine, fluorine or bromine, and in a broader sense includes iodine. Chlorine is preferred.

Step (a):

In reaction Step (a), the reductive amination is carried out in the presence of a reducing agent. A suitable reducing agent is a borohydride, which may also be in a complexed form, or hydrogen or a hydrogen donor both in the presence of a hydrogenation catalyst.

A suitable catalyst for the reductive amination with hydrogen or a hydrogen donor is, for example, nickel, such as Raney nickel, and noble metals or their derivatives, for example oxides, such as palladium, platinum or platinum oxide, which may be applied, if desired, to support materials, for example to carbon or calcium carbonate, for example, platinum on carbon. The hydrogenation with hydrogen or a hydrogen donor may preferably be carried out at pressures between 1 and about 100 atmosphere and at room temperature between about -80° to about 200°C, in particular between room temperature and about 100°C.

A preferred hydrogen donor is, for example, a system comprising 2-propanol and, if desired, a base, or, most preferably, formic acid or a salt thereof, e.g. an alkali metal, or tri-C<sub>1</sub>-C<sub>7</sub>-alkyl-ammonium salt thereof, for example, the sodium or the potassium salt thereof, if desired, in the presence of a tertiary amine, such as triethylamine. Further hydrogen donors comprise other alcohols such as ethanol, 2-methoxyethanol, benzyl alcohol, benzhydrol, pentan-2-ol, 1,2-ethandiol, 2,3-butandiol or cyclohexandiol, hydrazine, cyclohexene, cyclohexadiene, indane, tetralin, indoline, tetrahydroquinoline, hydroquinone, hypophosphinic acid or a suitable salt thereof such as the sodium salt thereof, sodium tetrahydroborate, sugars, ascorbic acid, limonene, or silanes. The hydrogen donor may also be used as solvent, especially 2-propanol or formic acid.

The reductive amination is preferably carried out under acidic, neutral or preferably under basic conditions. A suitable base comprises, for example, an alkali metal hydroxide or carbonate, such as sodium hydroxide, potassium hydroxide or potassium carbonate. Furthermore, an amine base can be used, for example, tri-C<sub>1</sub>-C<sub>7</sub>-alkylamine, such as triethylamine, tri-n-propylamine, tri-butylamine or ethyl-diisopropylamine, a piperidine, such as N-methylpiperidine, or a morpholine, such as N-methyl-morpholine. Preferred bases include lithium hydroxide, sodium hydroxide, sodium hydrogencarbonate, sodium carbonate, potassium hydrogencarbonate and potassium carbonate. Especially preferred is sodium hydroxide, sodium carbonate or tri-n-propylamine.

The reductive amination is carried out in a suitable inert solvent or a mixture of solvents including water. Inert solvents conventionally do not react with the corresponding starting materials of formulae (II a) and (II b). If an alkali metal borohydride such as sodium borohydride or lithium borohydride; an earth alkali metal borohydride such as calcium borohydride; an alkali metal cyanoborohydride, such as sodium cyanoborohydride or lithium cyanoborohydride, is used as reducing agent, for example, a polar solvent, for example, an alcohol such as methanol, ethanol, isopropanol or 2-methoxyethanol, or glyme, is preferred. If an alkali metal tri-(C<sub>1</sub>-C<sub>7</sub>-alkoxy)-borohydride such as sodium trimethoxy-ethoxy-borohydride; a tetra-C<sub>1</sub>-C<sub>7</sub>-alkylammonium-(cyano)borohydride such as tetrabutylammonium-borohydride or tetrabutylammonium-cyanoborohydride, is used as reducing agent, for example, hydrocarbons, such as toluene, esters such as ethylacetate or isopropylacetate, ethers such as tetrahydrofuran or tert-butylmethylether are preferred. If hydrogen or a hydrogen donor is used as reducing system, each in the presence of a hydrogenation

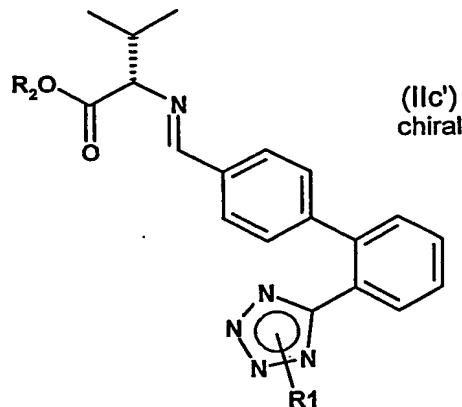
catalyst, a polar solvent is preferred. The reductive amination can also be carried out e.g. in a mixture of an organic solvent with water, both mono- and biphasic. In a biphasic system a phase transfer catalyst such as tetrabutylammoniumhalide, e.g. bromide, or benzyltrimethylammonium halide, e.g. chloride, may be added.

If  $R_1$  and  $R_2$  both represent a protecting group and if the compound of formula (IIb) is a free base, the presence of a base is not required. If, however,  $R_1$  is hydrogen and  $R_2$  is a protecting group, not more than a molar equivalent of a base may be added. In order to avoid racemisation, the reaction is preferably carried out by using less than an equimolar amount of a base.

The present invention likewise relates to novel compounds of formula (II a) that can be used as intermediates for the manufacture of the compound of formula (I).

The present invention likewise relates to novel compounds of formula (II b) that can be used as intermediates for the manufacture of the compound of formula (I).

The reaction of a compound of formula (II a) with a compound of formula (II b) results in an intermediately formed imine (Schiff base) of formula



that can, under certain reaction conditions, be isolated or that can be subjected to the reduction without isolation.

The reductive amination is a two-step reaction, the formation of an imine by removing water, followed by the reduction step. The removal is an equilibrium reaction, which can be directed to the formation of an imine by continuously eliminating the water, for example, by azeotropic removal.

If Step (a) is carried out via first manufacturing and isolating a compound of formula (II c'), a compound of formula (II a) is reacted with a compound of formula (II b), maybe in the presence of a base, if R<sub>1</sub> and/or R<sub>2</sub> are hydrogen. Compounds of formula (II c') can then be converted into corresponding compounds of formula (II c) by reducing the compounds of formula (II c') with a corresponding reducing agent as mentioned above.

The intermediate imine of formula (II c') can, for example, be isolated by removal of the solvent, e.g. by distillation, especially by azeotropic removal of water.

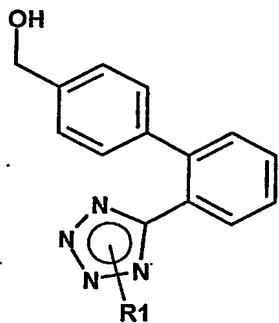
In a preferred variant, the reductive amination is carried out without isolating a compound of formula (II c').

In view of the imine structural element, compounds of formula (II c') comprise both the corresponding E and the corresponding Z isomer thereof. Preferred is the E isomer.

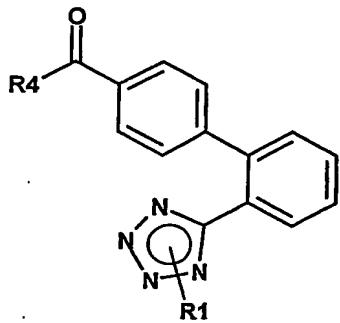
The present invention likewise relates to compounds of formula (II c') wherein R<sub>1</sub> is hydrogen or a tetrazole protecting group and wherein R<sub>2</sub> is hydrogen or a carboxy protecting group. Corresponding compounds can be used as intermediates for the manufacture of the compound of formula (I). Preferred are compounds of formula (II c'), wherein at least one of R<sub>1</sub> and R<sub>2</sub> represents hydrogen or both of R<sub>1</sub> and R<sub>2</sub> represent hydrogen.

~~The compounds of formulae (II a) and (II b) are partially known and can be prepared according to methods known per se.~~

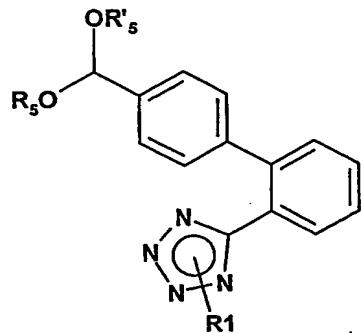
In another embodiment of the invention, reaction Step (a) can be combined with the formation of a compound of formula (II a) with the conventional oxidation of a corresponding hydroxymethyl derivative of formula



with the conventional reduction of a corresponding derivatives of the carboxylic acid of formula



wherein R<sub>4</sub> represents, for example, hydroxy, C<sub>1</sub>-C<sub>7</sub>-alkoxy or halogen such as chloro; or with the conventional hydrolysis of an acetal of formula



wherein  $R_5$  and  $R_5'$ , independently of one another, represent  $C_1$ - $C_7$ -alkyl, such as methyl or ethyl, or together form  $C_2$ - $C_4$ -alkylene, such as ethylene, propylene or butylene or 1,2-dimethylethylene.

The present invention likewise relates to reaction Step (a), especially the reduction step of reductive amination. If the reaction is carried out, for example, with a borohydride and under basic conditions in a polar solvent, optionally, in the presence of water, preferably in a lower (especially anhydrous) alkanol such as methanol, ethanol, isopropanol or glyme, the resulting compound of formula (II c) or (II c'), respectively, can surprisingly be obtained in an essentially enantiomerically pure form. It is expected that under basic conditions, normally an at least partial racemisation will take place. In contrast to this, surprisingly, for example, an enantiomer excess (ee) of a compound of formula (II c) or (II c'), respectively, of  $\geq 95\%$ , preferably  $\geq 98\%$  and most preferably  $\geq 99\%$  can be achieved.

Step (b):

In reaction Step (b), the acylation is carried out, for example, in absence or in presence of a suitable base.

Suitable bases are, for example, alkali metal hydroxides or carbonates, morpholine or piperidine amines, unsubstituted or substituted pyridines, anilines, naphthalene amines, tri- $C_1$ - $C_7$ -alkylamines, basic heterocycles or tetra- $C_1$ - $C_7$ -alkyl-ammonium hydroxides. Examples, which may be mentioned, include sodium hydroxide, potassium carbonate, triethylamine, tri-propyl-amine, tri-butyl-amine or ethyldiisopropylamine, N-methyl-morpholine or N-methyl-piperidine, dimethyl-aniline or dimethylamino-naphthalene, a lutidine, a collidine, or

benzyltrimethylammonium hydroxide. A preferred base is a tri-C<sub>1</sub>-C<sub>4</sub>-alkylamine such as ethyl-diisopropyl-amine or is pyridine.

The acylation is carried out in a suitable inert solvent or in a mixture of solvents. The person skilled in the art is fully enabled to select a suitable solvent or solvent system. For example, an aromatic hydrocarbon such as toluene, an ester such as ethylacetate or a mixture of ethylacetate and water, a halogenated hydrocarbon such as methylene chloride, a nitrile such as acetonitrile or propionitrile, an ether such as tetrahydrofuran or dioxane, 1,2-dimethoxy-ethane, amide such as dimethylformamide, or a hydrocarbon, such as toluene, is used as solvent.

During the acylation of a compound of formula (II c), if R<sub>2</sub> is hydrogen, the carboxyl-group might also be acylated forming a mixed anhydride. This intermediate is strongly prone to racemisation, mainly under basic conditions. Racemisation however can be avoided by first adding the compound of formula (II d), especially the halide, to the compound of formula (IIc) in a suitable inert solvent (e.g. dimethoxyethane, tetrahydrofuran or acetonitril), then slowly adding a sub-stoichiometric amount of the base, especially pyridine, in relation to the compound of formula (II d). Small amounts of water in the reaction mixture, preferably two equivalents, may additionally suppress racemisation.

The invention likewise relates to a compound of formula (II c), wherein R<sub>1</sub> is hydrogen or a tetrazole protecting group and R<sub>2</sub> is hydrogen or a carboxy protecting group, excluding a compound of formula (II c), wherein R<sub>1</sub> is ethyl and R<sub>2</sub> is trityl; that can be used e.g. as intermediate for the manufacture of the compound of formula (I).

The invention likewise relates to reaction Step (b). The resulting compound of formula (II e) can be obtained in an essentially enantiomerically pure form. For example, an enantiomer excess (ee) of a compound of formula (II c) or (II c'), respectively, of  $\geq 95\%$ , preferably  $\geq 98\%$  and most preferably  $\geq 99\%$  can be achieved.

If  $R_2$  represents a protecting group and  $R_1$  is hydrogen or a protecting group, for example, two equivalents of both a compound of formula (II d), e.g. the corresponding halide thereof, and a base, e.g. ethyl-diisopropyl-amine or tri-n-propylamine are added to a corresponding compound of formula (II c) dissolved in a suitable solvent, e.g. toluene. Surprisingly, no racemisation is observed.

Normally, in corresponding compounds of formula (II c), wherein  $R_2$  is hydrogen or a protecting group, one would expect at least partial racemisation, mainly in presence of base or acid and at elevated temperature. However, no racemisation is observed under the conditions applied according to this invention.

Normally, in corresponding compounds of formula (II c), wherein  $R_2$  is hydrogen, one would expect a racemisation. However, in a presence of a base, no racemisation is observed.

If  $R_1$  is hydrogen and  $R_2$  a protecting group, the tetrazole ring might also be acylated. When, however, the reaction mixture is quenched, for example with water or an alcohol such as methanol, the corresponding compound can be obtained wherein  $R_1$  is hydrogen.

Compounds of formula (II d) are known or can be manufactured according to methods known per se.

Step (c):

The removal of the protecting groups, both the tetrazole and carboxy protecting group, can be carried out according to methods known per se in the art.

For example, a benzylester can be converted into the corresponding acid especially by hydrogenation in the presence of a suitable hydrogenation catalyst. A suitable catalyst comprises, for example, nickel, such as Raney nickel, and noble metals or their derivatives, for example oxides, such as palladium or platinum oxide, which may be applied, if desired, to support materials, for example to carbon or calcium carbonate. The hydrogenation may preferably be carried out at pressures between 1 and about 100 atm. and at room temperature between

about -80° to about 200°C, in particular between room temperature and about 100°C.

The removal of a trityl or tert-butyl group, respectively, can be achieved by treating corresponding protected compounds with an acid, especially under mild conditions.

Step (d):

The isolation Step (d) of a compound of formula (I) is carried out according to conventional isolation methods, such as by crystallizing the resulting compound of formula (I) from the reaction mixture – if desired or necessary after work-up, especially by extraction - or by chromatography of the reaction mixture.

The conversion of an acid of formula (I) into a salt is carried out in a manner known per se. Thus, for example, a salt with a base of compounds of the formula (I) is obtained by treating the acid form with a base. Salts with a base can, on the other hand, be converted into the acid (free compound) in a customary manner, and salts with a base can be converted, for example, by treating with a suitable acid agent.

The present invention likewise relates to the novel compounds as described in the Working Examples part.

The following examples illustrate the invention described above; however, they are not intended to limit its extent in any manner.

Working Examples:

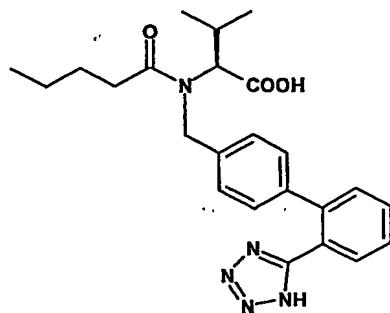
Example 1:

- a) Preparation of (S)-3-Methyl-2-((2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl)-amino)-butyric acid



Aqueous sodium hydroxide solution 2.0 M (approximately 100 ml; 200 mmol) is added to a stirred suspension of L-Valin (11.8 g; 100 mmol) and 2'-(1H-tetrazol-5-yl)-biphenyl-4-carbaldehyde (25.1 g; 100 mmol) in water (100 ml) at room temperature, until pH 11 is reached. The resulting clear solution is evaporated at 60°C in vacuo, and remaining water is azeotropically removed with 1-butanol. The residue (imine as a solid foam) is dissolved in absolute ethanol (300 ml), and sodium borohydride (3.78 g; 100 mmol) is added in portions to the solution at 0-5°C. The reaction mixture is stirred for 30 min at 0-5°C, and, if the reaction is complete (HPLC), quenched by addition of water (100 ml) and hydrochloric acid 2.0 M (80 ml; 160 mmol). The organic solvent (ethanol) is stripped off from the clear solution (pH 7) at 50°C in vacuo. The remaining aqueous concentrate is adjusted to pH 2 by slow addition of hydrochloric acid 2.0 M (approximately 70 ml; 140 mmol) at 40°C. During the addition the desired product precipitates. It is collected by filtration, washed with water and dried in vacuo. The crude product is suspended in methanol at 50°C, and the slurry is cooled to room temperature. (S)-3-methyl-2-((2'-(1H-tetrazol-5-yl)-biphenyl-4-yl)methyl)-butyric acid is collected by filtration and then dried in vacuo.

b) Preparation of (S)-3-Methyl-2-{pentanoyl-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl}-amino-butrylic acid



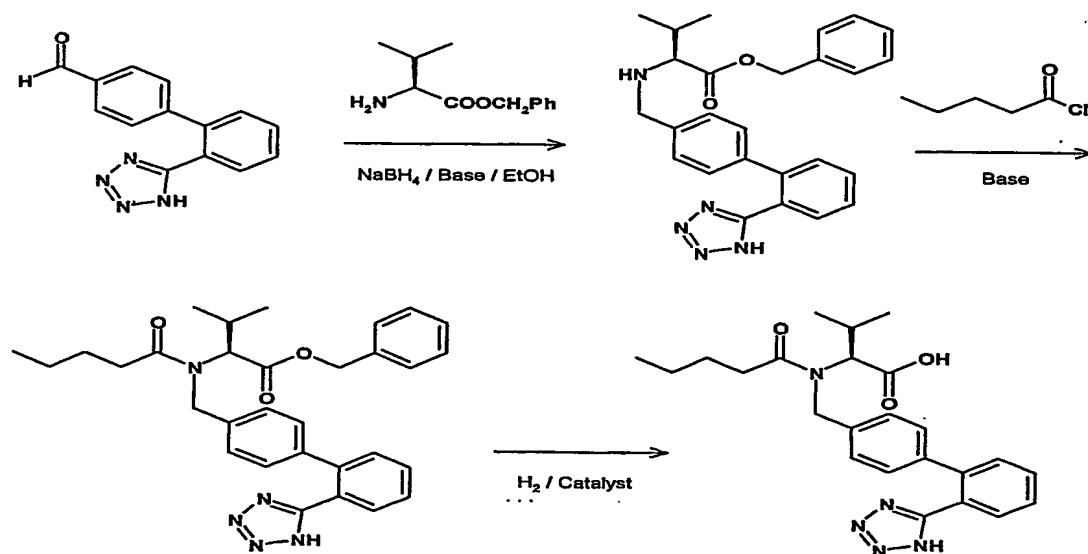
A suspension of (S)-3-methyl-2-((2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl)-amino)-butyric acid (17.6 g; 50.0 mmol) in 1,2-dimethoxyethan (116 g) is cooled to  $-5^{\circ}\text{C}$ , and valeroyl-chloride (9.9 ml; 80 mmol) is added, followed by slow addition of pyridine (6.0 ml; 75 mmol) diluted with 1,2-dimethoxyethane (60 ml). After completion of the reaction, the reaction mixture is quenched with methanol (18 ml). Finally water (50 ml) is added at room temperature, and after stirring for 1 h, the mixture is adjusted to pH 7.5 by addition of aqueous sodium carbonate solution 10% (~ 116 ml, 120 mmol) at  $0^{\circ}\text{C}$ . The organic solvents are stripped off at  $50^{\circ}\text{C}$  in vacuo. Ethylacetate (125 ml) is added to the remaining aqueous concentrate, and the two-phase system is adjusted to pH 2 at 0-5°C by addition of 2.0 M HCl (~ 98 ml). The organic phase is separated and concentrated at  $45^{\circ}\text{C}$  in vacuo (water is azeotropically removed). The crystallization of the product is initiated at  $45^{\circ}\text{C}$  and – after addition of cyclohexan (102 ml) – completed by cooling to  $-5^{\circ}\text{C}$ . The solid is collected by filtration, and after drying at  $50^{\circ}\text{C}$ , (S)-3-methyl-2-{pentanoyl-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amino}-butyric acid is received as a white powder.

Melting point: 108-110°C

Enantiomeric excess (by HPLC): ee > 99.5 %

Example 2:

This example can be illustrated by means of the following reaction scheme:



a) Preparation of (S)-3-Methyl-2-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}butyric acid benzylester

L-Valin-benzylester tosylate (6.38 g, 16.8 mmol) in toluene (40 ml) is extracted with a solution of sodiumcarbonate (2.36 g, 22.0 mmol) in water (40 ml). The organic phase (contains L-valin benzylester free base is separated, and 2'-(1H-tetrazol-5-yl)-biphenyl-4-carbaldehyde (4.13 g, 16.0 mmol) and tri-n-propyl-amine (3.20 ml, 16.8 mmol) are added at room temperature. The resulting solution is evaporated at 50°C in vacuo (water is removed azeotropically). The residual oil (containing the intermediate imine is dissolved in absolute ethanol (40 ml), and sodium borohydride (0.68 g, 17.6 mmol) is added in portions within 10 minutes (min.) at 0-5°C. The resulting solution is stirred for 30 min at 0-5°C. After completion of the reaction, the reaction mixture is quenched with water (10 ml) and adjusted to pH 6-7 by addition of hydrochloric acid 2 M (16 ml, 32 mmol) at RT. Ethanol is distilled off from the reaction mixture at 50° in vacuo and the residual aqueous mixture extracted with toluene (60 ml). The organic phase is concentrated at 50°C in vacuo to approximately 50 % of the original volume by destillation (water and ethanol are azeotropically removed). The resulting concentrate (35 ml) containing (S)-3-methyl-2-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}butyric acid benzylester is used as it is as starting material for the subsequent acylation step.

b) Preparation of (S)-3-Methyl-[2-pentanoyl-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}butyric acid benzylester

The solution of (S)-3-methyl-2-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}butyric acid benzylester (approximately 7.0 g , 16.0 mmol) in toluene (35 ml) from the previous step is diluted with toluene (35 ml). The clear solution is cooled to 0-5°C under anhydrous conditions, and N-ethyl-diisopropylamine (6.1 ml, 35.2 mol) and valeroylchloride (4.1 ml, 33.6 mmol) are added at this temperature. The reaction mixture is heated to 50°C within 30 min and agitated at 50°C for approximately 1 h and – after completion of the reaction - quenched by addition of methanol (10 ml) at 50°C. The clear solution is stirred for approximately 30 min at 50°C and finally cooled to RT. Water (30 ml) is added and the resulting two-phase system is adjusted to pH 2 by addition of hydrochloric acid 2.0 M (approximately 11 ml, 22 mmol). The organic phase is separated, extracted with water (30 ml) and concentrated at 50°C in vacuo to approximately 50 % of the original volume by destillation (water and methanol are azeotropically removed). The resulting concentrate in toluene (40 ml) is seeded at 40°C in order to start the crystallization and agitated at this temperature for

approximately 1 hour (h). The suspension is gradually cooled to 0°C within 6-10 h. The solid is separated by filtration, washed with cold toluene (30 ml) and dried in vacuo at 50°C to give (S)-3-methyl-{2-pentanoyl-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid benzylester.

Melting point: 115 - 116°C

Enantiomeric excess (by HPLC): ee > 99.8 %

c) Preparation of (S)-3-Methyl-2-{pentanoyl-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid

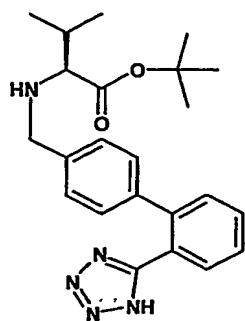
A solution of (S)-3-Methyl-{2-pentanoyl-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid benzylester (10.6 g; 20.0 mmol) in Ethylacetate (43 ml) is hydrogenated at 4 bar / 50°C in presence of a wet palladium on charcoal catalyst 5% (1.12 g, containing 50 % water). After completion of the reaction (cease of hydrogen consumption) the catalyst is removed by filtration and the filtrate is concentrated at 45°C in vacuo (water is azeotropically removed). The crystallization of the product is initiated at 45°C and – after addition of cyclohexan (102 ml) – completed by cooling to -5°C. The solid is collected by filtration, and after drying at 50°C, (S)-3-methyl-2-{pentanoyl-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino} -butyric acid is received as a white powder.

Melting point: 108-110°C.

Enantiomeric excess (by HPLC): ee > 99.5 %

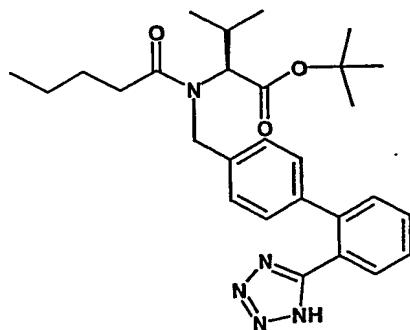
Example 3:

a) Preparation of (S)-3-Methyl-2-((2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl)-amino)-butyric acid tert-butylester



To a suspension of L-valine tert-butylerster hydrochloride (419.4 mg; 2 mmol) in 5 ml of isopropylacetate is added sodium carbonate (265 mg; 2.5 mmol) in 5 ml of water. After complete dissolution, the two phases are separated immediately. The aqueous layer is washed once with 4ml of isopropylacetate. The combined organic layers are washed with 5 mL of water. The colourless organic is dried over sodium sulfate, filtered, evaporated in vacuum and dried in high vacuum to give a colourless oil. The oil is dissolved in 4 ml of methanol. After addition of the 2'-(1H-tetrazol-2-yl)-biphenyl-4-carbaldehyde (515 mg; 2mmol) and triethylamine (0.278 ml; 2 mmol), the yellow solution is stirred for 5 minutes before evaporation in vacuum to give a yellow oil. After dissolution in 4 ml ethanol the solution is cooled to 0°C. Sodiumborohydride (78 mg; 2 mmol) is added in 4 portions with stirring until the imine dissapeared (HPLC). The slightly yellow solution is acidified from pH 11 to pH 6 with 3.2 ml of a 1.0 M HCl solution. Evaporation of the ethanol affords a mixture of a yellow oil in water. This mixture is extracted with isopropylacetate. The combined organic layers are dried over sodium sulfate, filtered, evaporated in vacuum and dried in high vacuum to give (S)-3-methyl-2-((2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl)-amino)-butyric acid tert-butylerster as an oil.

b) Preparation of (S)-3-Methyl-{2-pentanoyl-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid tert-butylerster



(S)-3-methyl-2-((2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl)-amino)-butyric acid tert-butylerster (8.5 g; ~16.0 mmol) is dissolved in toluene (63 ml) and N-ethyl-diisopropylamine (6.1 ml; 35.2 mmol) and valeroylchloride (4.1 ml; 33.6 mmol) are added at RT. The clear solution is heated to 50°C and stirred at this temperature for 60 min. After completion of the reaction, the reaction mixture is quenched with methanol (10 ml) at 50°C, and finally, water is added at RT. The two-phase system is adjusted to pH 2 by addition of 2.0 M HCl (~ 5 ml). The organic phase is separated and concentrated at 50°C in vacuo (remaining water is removed

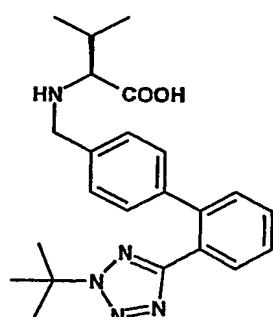
azeotropically). On cooling to RT, the product starts to crystallize from toluene. (S)-3-methyl-{2-pentanoyl-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl-methyl]-amino}-butyric acid tert-butyl-ester is received as a white powder after filtration and drying in vacuo.

Melting point: 153.4°C

Enantiomeric excess (by HPLC): ee > 99.8 %

Example 4:

a) Preparation of (S)-2-((2"-tert-Butyl-tetrazol-5"-yl)-biphenyl-4-ylmethyl)-amino)-3-methyl-butyric acid

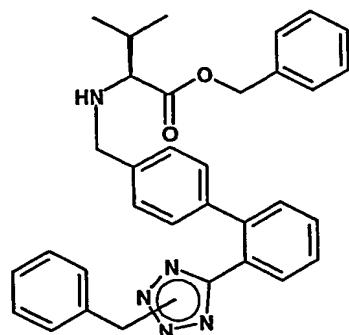


A soda solution (1 mol/l; 1.0 ml, 1.0 mmol) is added to L-valine (117.15 mg; 1.0 mmol). After complete dissolution, the reaction is evaporated. To the white solid is added 2'-(1H-tert-butyl-tetrazol-2-yl)-biphenyl-4-carbaldehyde (306.4 mg, 1 mmol) and 4 ml of methanol. After complete dissolution the reaction is evaporated and the slightly yellow oil is dried in high vacuum. The imine is dissolved in 4 ml ethanol and cooled to 0°C before sodium borohydride (38 mg; 1.0 mmol) is added in 2 portions with stirring until the imine disappeared. The slightly yellow solution is acidified with 1,8 ml of a 1N HCl solution to pH 6-7. Evaporation in vacuum affords a white solid. 10 ml of isopropylacetate and 10mL water are added. The white precipitate is filtered, washed with water and dried to result in 2-((2"-tert-butyl-tetrazol-5"-yl)-biphenyl-4-ylmethyl)-amino)-3-methyl-butyric acid.

Melting point: 189.7°C

Example 5:

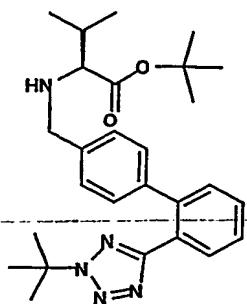
a) Preparation (S)-2-[(2'-(2-Benzyl-2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amino}-3-methylbutyric acid benzyl ester



L-Valin-benzyl ester tosylate (0.97 mmol, 368 mg) is suspended in isopropylacetate (4 ml). To this suspension was added a solution of sodium carbonate (1.21 mmol, 128 mg) in water (2 ml) at room temperature. The resultant mixture is agitated for 2 minutes, transferred to a separating funnel and the phases separated. The organic phase is dried over sodium sulphate, filtered and concentrated in vacuo to afford the free base as a colourless oil. The 2'-(1H-benzyl-tetrazol-2-yl)-biphenyl-4-carbaldehyde (0.88 mmol, 300 mg) is dissolved in 1,2-dimethoxyethane (4 ml) at room temperature and the resultant solution added to the free base residue. After 8 hours the solvent is removed in vacuo and the residue dissolved in ethanol (4 ml). Sodium borohydride (1.1 mmol, 41.6 mg) is added to the reaction mixture. The resultant opaque solution is stirred at room temperature for more than 2 hours and then concentrated in vacuo to remove the ethanol. Water (20 ml) and dichloromethane (20 ml) are added and the aqueous phase pH is adjusted to 1 by addition of 1N HCl. The phases are separated and the aqueous phase extracted again with dichloromethane (10 ml). The combined organic phases are washed with water (10 ml), dried over anhydrous sodium sulphate, filtered and concentrated in vacuo to afford the title compound as a colourless oil.

Example 6:

a) Preparation of (S)-2-[(2'-(2-tert-Butyl-2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amino}-3-methylbutyric acid tert-butyl ester



L-Valin-t-butyl ester hydrochloride (1.32 mmol, 278 mg) is suspended in isopropylacetate (5 ml). To this suspension was added a solution of sodium carbonate (1.65 mmol, 175 mg) in water (5 ml) at room temperature. The resultant mixture is agitated for 2 minutes, transferred to a separating funnel and the phases separated. The organic phase is dried over sodium sulphate, filtered and concentrated in vacuo to afford the free base as a colourless oil.

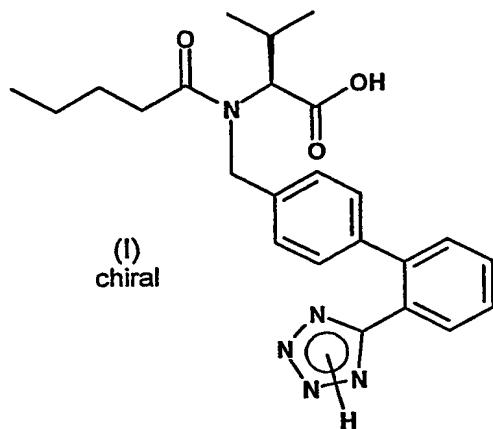
The 2'-(1H-tert.-butyl-tetrazol-2-yl)-biphenyl-4-carbaldehyde (1.2 mmol, 367.2 mg) is dissolved in ethanol (5 ml) at room temperature and the resultant solution added to the free base residue. After 90 minutes sodium borohydride (1.5 mmol, 56.7 mg) is added to the reaction mixture. The resultant opaque solution is stirred at room temperature for 2 hours and then concentrated in vacuo to remove the ethanol. Water (20ml) and dichloromethane (20 ml) are added and the aqueous phase pH is adjusted to 1 by addition of 1N HCl. The phases are separated and the aqueous phase extracted again with dichloromethane (10 ml). The combined organic phases are washed with water (10 ml), dried over anhydrous sodium sulphate, filtered and concentrated in vacuo to afford the title compound as a colourless oil.

<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400MHz):

$\delta$ =7.86 (1H, d, J=8 Hz), 7.41-7.68 (3H, m), 7.44 (2H, d, J=8Hz), 7.24 (2H, d, J=8Hz), 4.17 (1H, d, J=13Hz), 4.08 (1H, d, J=13Hz), 3.56 (1H, d, J=2Hz), 2.27 (1H, m), 1.12 (3H, d, J=7Hz) and 1.06 (3H, d, J=7Hz).

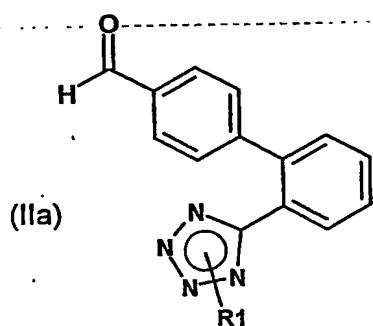
What is claimed is:

1. A process for the manufacture of the compound of formula (I)

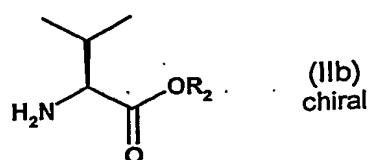


or a salt thereof, comprising

- (a) reacting a compound of formula (II a)

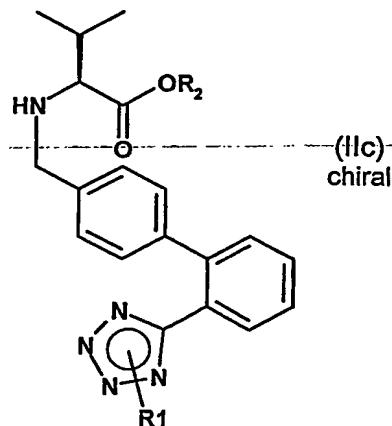


or a salt thereof, wherein R<sub>1</sub> is hydrogen or a tetrazole protecting group, with a compound of formula

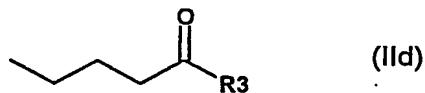


or a salt thereof, wherein  $R_2$  represents hydrogen or a carboxy protecting group, under the conditions of a reductive amination; and

(b) acylating a resulting compound of formula (II c)

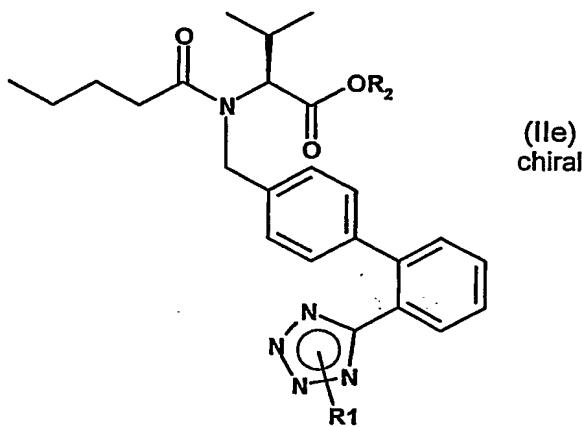


or a salt thereof with a compound of formula (II d)



wherein  $R_3$  is an activating group; and,

(c) if  $R_1$  and/or  $R_2$  are different from hydrogen, removing the protecting group(s) in a resulting compound of formula (II e)



or a salt thereof; and

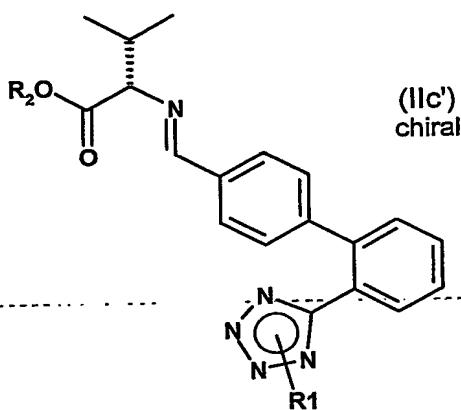
(d) isolating a resulting compound of formula (I) or a salt thereof; and, if desired, converting a resulting free acid of formula (I) into a salt thereof or converting a resulting salt

of a compound of formula (I) into the free acid of formula (I) or converting a resulting salt of a compound of formula (I) into a different salt.

2. The process according to claim 1, wherein in compounds of formulae (II a), (II b), (II c), and (II e) R<sub>1</sub> represents hydrogen and R<sub>2</sub> represents hydrogen and wherein in compounds of formula (II d) R<sub>3</sub> represents halogen.

3. The process according to claim 1 or 2, wherein the reductive amination is carried out in the presence of a reducing agent such as a borohydride, which may also be in complexed form, or hydrogen or a hydrogen donor both in the presence of a hydrogenation catalyst.

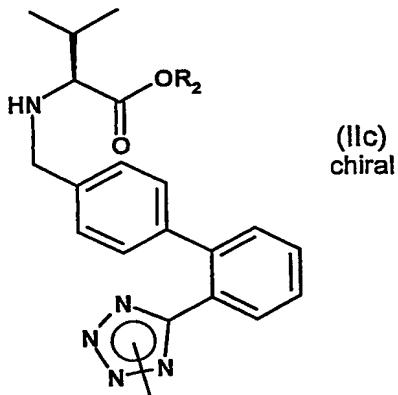
4. The process according to claim 1 or 2, wherein step (a) is carried out by first forming an imine of formula



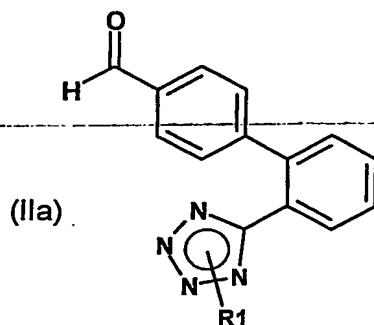
by condensing compounds of formulae (II a) and (II b) and by removing water and then followed by reducing a compound of formula (IIc') in the presence of a reducing agent.

5. The process according to claim 1 or 2, wherein step (b) is carried out by first adding a compound of formula (II d) to a compound of formula (II c) and then slowly adding a sub-stoichiometric amount of a base in relation to the compound of formula (II d).

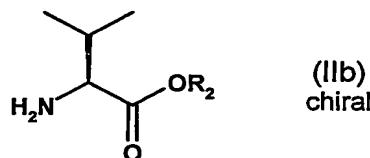
6. A process for the manufacture of a compound of formula



wherein R<sub>1</sub> represents hydrogen or a tetrazole protecting group and R<sub>2</sub> represents hydrogen or a carboxy protecting group,  
 comprising reacting a compound of formula (II a)

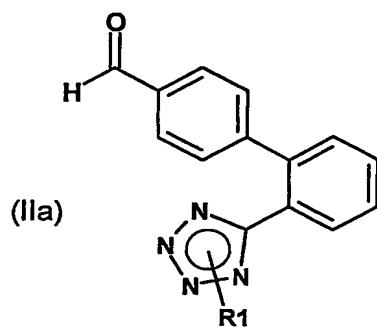


or a salt thereof, wherein R<sub>1</sub> is hydrogen or a tetrazole protecting group, with a compound of formula

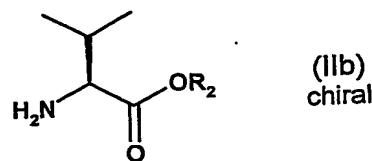


---or a salt thereof, wherein R<sub>2</sub> represents hydrogen or a carboxy protecting group, under the conditions of a reductive amination.

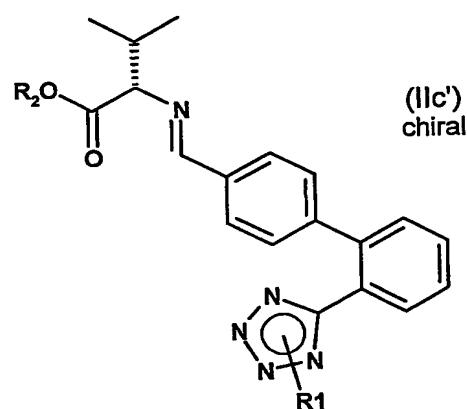
7. A process according to claim 6, comprising reacting a compound of formula (II a)



or a salt thereof, wherein R<sub>1</sub> is hydrogen or a tetrazole protecting group, with a compound of formula

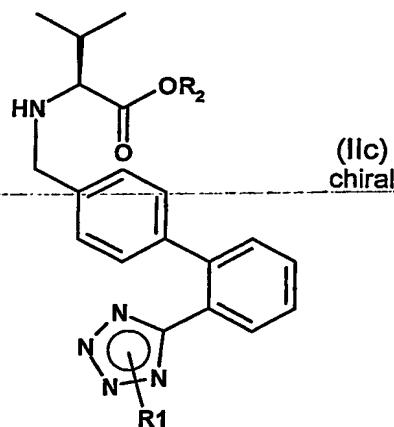


or a salt thereof, wherein R<sub>2</sub> represents hydrogen or a carboxy protecting group, while eliminating water, and reducing a resulting compound of formula (II c')



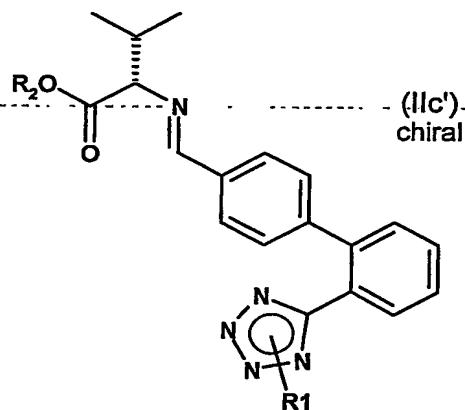
in the presence of a reducing agent.

## 8. A compound of formula



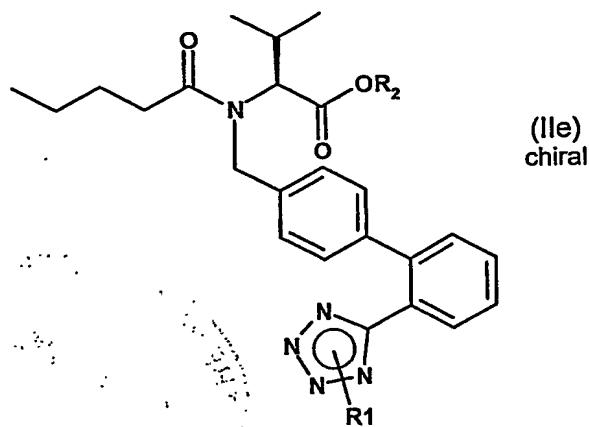
wherein R<sub>1</sub> is hydrogen or a tetrazole protecting group and R<sub>2</sub> is hydrogen or a carboxy protecting group, excluding a compound of formula (II c) wherein R<sub>1</sub> is ethyl and R<sub>2</sub> is trityl.

## 9. A compound of formula



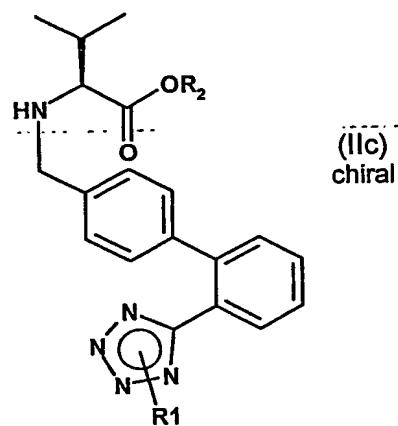
wherein R<sub>1</sub> is hydrogen or a tetrazole protecting group and R<sub>2</sub> is hydrogen or a carboxy protecting group.

## 10. A process for the manufacture of a compound of formula

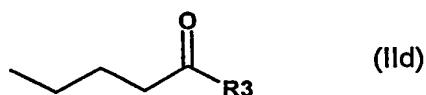


wherein R<sub>1</sub> represents hydrogen or a tetrazole protecting group and R<sub>2</sub> represents hydrogen or a carboxy protecting group,

comprising acylating a resulting compound of formula (II c)



or a salt thereof with a compound of formula (II d)



wherein R<sub>3</sub> is an activating group.

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